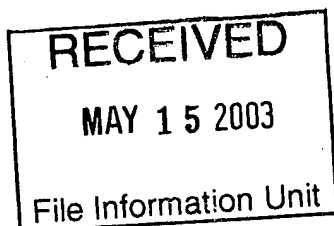


REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of <i>Singer et al</i>	
Application Number <i>09/552,485</i>	Filed <i>4-18-00</i>
Art Unit	Examiner

Paper No. *#24*

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☒ (A) referred to in:

United States Patent Application Publication No. *2003/0088094*, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

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☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

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2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Anne Murphy
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Anne MURPHY
Typed or printed name

5-15-03

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(initials)

Unit File Information Unit



US 20030088094A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0088094 A1**
(43) **Pub. Date: May 8, 2003**
Singer et al.(54) **NOVEL SYNTHESIS AND
CRYSTALLIZATION OF PIPERAZINE
RING-CONTAINING COMPOUNDS**(52) **U.S. Cl. 540/578; 544/360**(76) **Inventors: Claude Singer, Kfar Saba (IL); Anita
Liberman, Tel Aviv (IL); Nina
Finkelstein, Herzliya (IL)**(57) **ABSTRACT**

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The present invention is directed to methods for the preparation of piperazine ring-containing compounds, particularly mirtazapine. According to the present invention, the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine is made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with a base where the base is present in a ratio of up to about 12 moles of the base per one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine. The mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with potassium hydroxide at a temperature of at least about 130° C. The method of the present invention also includes reacting 2-amino-3-hydroxymethyl pyridine with N-methyl-1-phenyl-2,2'-iminodiethyl chloride to form 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl piperazine, and adding sulfuric acid to the 1-(3-hydroxymethylpyridyl-2)-phenyl-4-methylpiperazine to form mirtazapine. The present invention also relates to new processes for recrystallization of mirtazapine from crude mirtazapine.

(21) **Appl. No.: 10/283,093**(22) **Filed: Oct. 30, 2002****Related U.S. Application Data**(62) **Division of application No. 09/900,646, filed on Jul.
6, 2001, which is a division of application No.
09/552,485, filed on Apr. 18, 2000**(60) **Provisional application No. 60/130,047, filed on Apr.
19, 1999.****Publication Classification**(51) **Int. Cl.⁷ C07D 487/22; C07D 43/04**